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### BRIEF COMMUNICATION

## A case-control association study between Obsessive-Compulsive Disorder (OCD) and the MCP-1 -2518G/A polymorphism in a Chinese sample

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#### DESCRIPTORS:

MCP-1 -2518G/A  
Polymorphism;  
OCD;  
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Association Analysis

#### Abstract

**Objective:** To investigate the association between Obsessive-Compulsive Disorder (OCD) and a functional polymorphism of MCP-1 in the Chinese Han population. **Method:** We genotyped and performed a case-control association analysis of the MCP-1 -2518G/A polymorphism in 200 OCD patients and 294 healthy control subjects. **Results:** There was no significant difference in MCP-1 -2518G/A genotypic and allelic frequencies between OCD cases and controls ( $\chi^2 = 1.123$ ,  $df = 2$ ,  $P = 0.57$  by genotype;  $\chi^2 = 0.802$ ,  $df = 1$ ,  $P = 0.37$  by allele). **Conclusions:** Our results indicated that MCP-1 -2518G/A may not play a major role in the genetic predisposition of the Chinese Han population to OCD. However, further studies using a larger number of subjects are required to obtain a clear conclusion.

**DESCRIPTORES:**

Polimorfismo  
MCP-1 -2518G/A;  
TOC;  
Citocina;  
Análise de Associações

## Estudo de associação de casos-controle entre Transtorno Obsessivo-Compulsivo (TOC) e polimorfismo MCP-1 -2518G/A em uma coorte chinesa

**Resumo**

**Objetivo:** Investigar a relação entre Transtorno Obsessivo-Compulsivo (TOC) e um polimorfismo funcional de MCP-1 na população chinesa de etnia Han. **Métodos:** Determinamos os genótipos e realizamos uma análise de associações de casos-controle de polimorfismo MCP-1 -2518G/A em 200 indivíduos com TOC e 294 indivíduos saudáveis (controle). **Resultados:** Não houve diferença significativa no genótipo MCP-1 -2518G/A e nas frequências alélicas entre casos de TOC e controles ( $\chi^2 = 1,123$ ,  $df = 2$ ,  $P = 0,57$  por genótipo;  $\chi^2 = 0,802$ ,  $df = 1$ ,  $P = 0,37$  por alelo). **Conclusões:** Nossos resultados indicaram que MCP-1 -2518G/A pode não ter grande participação na predisposição genética da etnia Han no que diz respeito ao TOC. Contudo, novos estudos com um maior número de indivíduos são necessários para uma conclusão mais clara.

## Introduction

Obsessive-Compulsive Disorder (OCD) is a mental disorder characterized by repetitive, obsessive thinking and compulsive behavior. Its lifetime prevalence is 1.9-3.3%,<sup>1</sup> which makes OCD the fourth most common mental disorder behind phobias, substance dependence, and major depression. In the last several years, a number of studies have found an association between OCD and proinflammatory cytokines such as TNF- $\alpha$  and interleukin-10, as well as natural-killer and T-cell function.<sup>2-3</sup>

Mainly derived from perivascular astrocytes, monocyte chemoattractant protein 1 (MCP-1) increases blood brain barrier (BBB) permeability and attracts leukocytes across the BBB, which possibly draws autoantibodies in the serum of OCD patients to the basal ganglia.<sup>4</sup> When associated with the BBB endothelium, MCP-1 plays a role in mediating: 1.) the differentiation of neural stem cells into neurons, astrocytes and oligodendrocytes and 2.) the regulation of adult subventricular zone-derived progenitor cell migration after striatal cell death.<sup>5</sup> Together, these roles indicate an intimate association between neurodevelopmental and neuroregenerative processes regulated by inflammatory mediators. The MCP-1 -2518G/A polymorphism may affect the transcriptional activity of monocyte MCP-1 production and the severity of organ inflammation.<sup>6</sup>

We hypothesized that MCP-1 might increase the risk of OCD. We performed an association study between OCD and the 2518G/A polymorphism of MCP-1 to examine the hypothesis that this functional variant may influence the etiology of OCD in a Chinese Han population.

## Materials and Methods

### Study Population

A total of 200 OCD patients [mean age = 28.92 years and SD = 10.85 years; 35.6% females; 64.4% males mean age of onset = 19.75 years and SD = 10.72 years; 25.4% early onset (< 17 years old); mean duration of the disorder = 10.84 years and SD = 8.65 years] and 294 healthy control subjects [mean age = 30.52 years and SD = 9.65 years; 34.8% females;

65.2% males] were recruited from the Affiliated Hospital of Medical College, Qingdao University. All of the patients were diagnosed according to DSM-IV diagnostic criteria. Probands with a history of neurologic or metabolic diseases, bipolar or psychotic disorder, or current substance dependence were excluded. Control subjects were selected from among healthy volunteers from Qingdao University, and all had no history of any psychiatric disorder. The Ethics Committees of Qingdao University Medical College Hospital approved the study, and all of the subjects provided written informed consent.

### DNA analysis and statistical analysis

Genomic DNA was extracted from peripheral blood leukocytes using standard methods. The polymorphism at 2518G/A in the promoter region of MCP-1 was genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) according to the procedure described by Kuroda et al.<sup>7</sup> The sequences of several PCR products were verified by direct sequencing. A case-control study was performed using the chi-square test of homogeneity.

## Results

According to Hardy-Weinberg equilibrium, the genotypic distribution was not significantly different from the expected distribution in OCD patients ( $\chi^2 = 0.056$  with 1 df and  $P = 0.81$ ) and controls ( $\chi^2 = 0.413$  with 1 df and  $P = 0.52$ ). No significant differences were found in 2518G/A genotypic and allelic frequencies between OCD cases and controls ( $\chi^2 = 1.123$ ,  $df = 2$ ,  $P = 0.57$  by genotype;  $\chi^2 = 0.802$ ,  $df = 1$ ,  $P = 0.37$  by allele) (Table 1).

## Discussion

A number of studies have demonstrated a connection between OCD and infections, thus indicating the existence of possible immune dysfunction in OCD.<sup>8</sup> Consequently, many interesting candidate genes encoding cytoactive material, such as inflammatory factors, warrant investigation, and a series of studies has already been performed. Unfortunately, the results of these studies were quite inconsistent. Konuk and colleagues found a significant increase in the plasma levels of TNF- $\alpha$

**Table 1** Genotype distribution and relative allele frequencies of the MCP-1 -2518G/A polymorphism in Chinese individuals with (n = 200) or without (n = 294) OCD

Group	No	Genotype frequency (%)			Allele frequency (%)	
		G/G	G/A	A/A	G	A
OCD	200	70 (0.350)	98 (0.490)	32 (0.160)	238 (59.5)	162 (40.5)
Controls	294	97 (0.330)	139 (0.473)	58 (0.197)	333 (56.6)	255 (43.4)

and IL-6 in OCD patients compared with healthy controls.<sup>9</sup> As mentioned above, MCP-1 is a critical chemokine that is closely associated with neuroinflammatory conditions of various etiologies, while its deficiency protects against inflammation in the brain.<sup>10</sup> We hypothesized that MCP-1 could increase the risk of OCD, but there has been no evidence supporting our hypothesis to date. This is the first report investigating a single nucleotide polymorphism in MCP-1 in relation to OCD. Our results showed no significant differences in -2518G/A genotypic and allelic frequencies between 200 OCD cases and 294 controls. It is unlikely that this result is due to quality control issues as the experiment was carefully designed, we used proper equipment that had a high accuracy, and the sequences of several PCR products were verified by direct sequencing. The patient and control samples were chosen carefully and randomly, and those individuals who had mental disabilities, drug and/or alcohol dependence, or metabolic, psychiatric, or neurological diseases were excluded. The genetic background of the sample was also strictly considered. However, the following reasons could explain our negative results. The most likely reason is low power due to limited sample size (only 14.8%). Additionally, MCP-1 could play only a minor role, thus contributing only a small increase in risk that could be undetectable due to the small sample size. Moreover, the onset age of OCD and the rate of patients with an earlier onset of OCD could not be excluded. Therefore, further research targeting other populations should be performed, which would provide a better understanding of MCP-1 expression functionality.

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## Disclosures

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\* Modest

\*\* Significant

\*\*\* Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.

## References

1. Karno M, Golding JM, Sorenson SB, Burnam MA. The epidemiology of obsessive-compulsive disorder in five US communities. *Arch Gen Psychiatry*. 1988;45(12):1094-9.
2. Denys D, Fluitman S, Kavelaars A, Heijnen C, Westenberg H. Decreased TNF-alpha and NK activity in obsessive-compulsive disorder. *Psychoneuroendocrinology*. 2004;29(7):945-52.
3. Hounie AG, Cappi C, Cordeiro Q, Sampaio AS, Moraes I, Rosário MC, Palácios SA, Goldberg AC, Vallada HP, Machado-Lima A, Nakano E, Kalil J, Pauls D, Pereira CA, Guilherme L, Miguel EC. TNF-alpha polymorphisms are associated with obsessive-compulsive disorder. *Neurosci Lett*. 2008;442(2):86-90.
4. Lawrence DM, Seth P, Durham L, Diaz F, Boursiquot R, Ransohoff RM, Major EO. Astrocyte differentiation selectively upregulates CCL2/monocyte chemoattractant protein-1 in cultured human brain-derived progenitor cells. *Glia*. 2006;53(1):81-91.
5. Gordon RJ, McGregor AL, Connor B. Chemokines direct neural progenitor cell migration following striatal cell loss. *Mol Cell Neurosci*. 2009;41(2):219-32.
6. Rovin BH, Lu L, Saxena R. A novel polymorphism in the MCP-1 gene regulatory region that influences MCP-1 expression. *Biochem Biophys Res Commun*. 1999;259(2):344-8.
7. Kuroda S, Puri P. Lack of association of IL8 gene polymorphisms with familial vesico-ureteral reflux. *Pediatr Surg Int*. 2007;23(5):441-5.
8. Murphy TK, Sajid MW, Goodman WK. Immunology of obsessive-compulsive disorder. *Psychiatr Clin North Am*. 2006;29(2):445-69.
9. Konuk N, Tekin IO, Ozturk U, Atik L, Atasoy N, Bektas S, Erdogan A. Plasma levels of tumor necrosis factor-alpha and interleukin-6 in obsessive compulsive disorder. *Mediators Inflamm*. 2007:[epub]65704.
10. Thompson WL, Karpus WJ, Van Eldik LJ. MCP-1-deficient mice show reduced neuroinflammatory responses and increased peripheral inflammatory responses to peripheral endotoxin insult. *J Neuroinflammation*. 2008;5:35.